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EXAMINER

NEGIN, RUSSELL SCOTT

ART UNIT

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1631

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/615,116	Applicant(s) COLEMAN ET AL.	
	Examiner Russell S. Negin	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-60 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-60 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____ | 6) <input type="checkbox"/> Other: ____ |

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-13, 17-20, 22-23, 28-33, 37-38, 43-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Gerlyng et al. [Cytometry, volume 13, 1992, pages 404-415].

Claims 1-13, 17-20, 22-23, 28-33, 37-38, 43-47 state:

1. A method for identifying bi-nuclear cells, comprising:
 capturing at least a first image of a plurality of marked cells;
 processing the first image to obtain at least a first feature for each of the plurality of cells; analyzing the first features for the plurality of cells to determine whether the first feature is indicative of a bi-nuclear cell; and
 identifying those cells for which the first feature is indicative of a bi-nuclear cell as being a bi-nuclear cell.
2. The method as claimed in claim 1, in which the first feature is a nuclear feature.
3. The method as claimed in claim 2, in which the first feature is a nuclear morphology.
4. The method as claimed in claim 3, in which analyzing the nuclear morphology further includes determining the number of nuclei present in the first feature.
5. The method as claimed in claim 4, in which analyzing the nuclear morphology includes identifying concave regions in the periphery of the shape of the nuclear feature.
6. The method as claimed in claim 5, in which cells are identified as being bi-nuclear if more than one concave region is identified.
7. The method as claimed in claim 2, in which analysing the first feature further includes analysing the spatial distribution of the first feature.

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8. The method as claimed in claim 7, in which analysing the first feature further includes identifying at least one pair of first features.

9. The method as claimed in claim 8, further including:
processing the first image to obtain a second feature indicative of a cytoplasmic component; and
wherein analyzing further comprises assessing the cytoplasmic component between the pair of first features.

10. The method as claimed in claim 9, in which identifying further comprises determining whether the amount of the cytoplasmic component exceeds a threshold value.

11. The method as claimed in claim 10, in which the threshold value relates to a control group of cells.

12. The method as claimed in claim 7, and further comprising identifying pairs of nearest neighbour first features.

13. The method as claimed in claim 12, and further comprising identifying the next nearest neighbour first features to a pair of nearest neighbour first features.

17. A method for assessing the affect of a treatment on a cell, comprising:
exposing a population of cells to the treatment; capturing an image of a plurality of cells from the population;
obtaining a plurality of cellular features from the image;
analyzing the plurality of cellular features to assess a property of the cellular feature characteristic of bi-nuclear cells; and determining the abundance of bi-nuclear cells.

18. A method as claimed in claim 17, and further comprising classifying the treatment based on the abundance of bi-nuclear cells.

19. A method as claimed in claim 17, in which the plurality of cellular features includes nuclear features.

20. A method as claimed in claim 19, in which the plurality of cellular features further includes cytoplasmic features.

21. A method as claimed in claim 18, wherein the treatment is classified in terms of its affect on cytokinesis.

22. A method as claimed in claim 18, further comprising applying a statistical test to the abundance of bi-nuclear cells in the treated cell population and the abundance of bi-

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nuclear cells in a control population in order to determine the significance of the affect of the treatment on the treated cell population.

23. A method for characterising cells, comprising: determining, from a captured image of a nuclear component of a plurality of cells, the number of concave portions in the outline of the image of the nuclear component; and characterising the cell based on the number of concave portions.

30. The method as claimed in claim 23, wherein the cell is characterised as multi-nuclear if more than two concave portions are identified.

31. The method as claimed in claim 23, wherein characterising the cell further includes assessing a further feature of a nuclear image of the nuclear component

32. The method as claimed in claim 31, wherein the further feature of the image of the nuclear component is the total intensity of the image of the nuclear component.

33. The method as claimed in claim 32, wherein the cell is characterised as multinucleate if there are two or more concave portions and the total intensity exceeds a first threshold.

37. A method of identifying bi-nuclear cells, comprising:
 identifying, from a captured image of a nuclear component of a plurality of cells, at least one pair of nuclear components;
 determining, from a captured image of a cytoplasmic component of the plurality of cells, a measure of the amount of the cytoplasmic component interposed between the pair of nuclear components; and
 characterising the cells based on the measure of the amount of the cytoplasmic component.

38. The method as claimed in claim 37, wherein the measure is the detected intensity of the image of the cytoplasmic component.

43. The method as claimed in claim 37, further including removing particular nuclear components from the image prior to identifying pairs.

44. The method as claimed in claim 43, wherein the particular nuclear components are selected from the group comprising: nuclear components of mitotic cells; nuclear components at the edge of the image; multinucleate nuclear components; nuclear components having an image intensity exceeding a threshold; and nuclear components having an image intensity below a threshold.

45. The method as claimed in claim 37, wherein characterising the cells further includes comparing the measure of the amount of the cytoplasmic component with a measure of

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the amount of the same cytoplasmic component for a control group of cells.

46. The method as claimed in claim 45, wherein the measure of the amount for the control group corresponds to the proportion of bi-nuclear cells expected in the control group.

47. The method as claimed in claim 46, wherein the proportion of bi-nuclear cells expected in the control group is not more than 4%.

In Gerlyng et al. Figure 1A and Table 1, the authors describe a method for identifying bi-nuclear cells by capturing an image of a plurality of marked cells. As stated on page 406, column 1, lines 22-30 and lines 34-38, "The cell monolayers were subsequently analyzed by transferring the microscope image from a Zeiss axioplan microscope equipped with a x 40 objective and a 546 nm green filter to a SEP-IPS image processing unit (Kontron, Munich, Germany) using a Grundig FA 76 video camera. The nuclear boundaries were defined by the operator by establishing a threshold grey level for each image, and pixels darker than this threshold value were identified as belonging to a nucleus.... Visual identification in the grey level image and also in the microscope directly allowed the precise identification of cell types and also classification of nuclei as belonging to mononuclear or binuclear hepatocytes." Table 1 represents a processing and analysis of Figure 1A.

The features identified in Figure 1A of Geryling et al are nuclear features with given morphologies from which nuclei can be identified. Figure 1 allows the identification of nuclei not only from the staining, but also the presence of concave regions around each black nucleus. In bi-nuclear cells, where two nuclei are clustered, the bi-nucleus is represented by more than one concave region in which the spatial

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distribution of the nuclei represents whether a binucleus exists. The proximity of the two stained regions and the number of concave regions around the nuclei (i.e. nearest neighbour first features) indicates the presence of a binucleus. In addition, next nearest neighbor regions in Figure 1A were identified visually to determine the presence of multinuclear features.

The non-stained regions of Figure 1A indicate the presence of a cytoplasmic region. The absence of a cytoplasmic region between two stained nuclei indicates the presence of a binucleus. In other words, Figure 1A is used as a measure of the cytoplasmic components of the cells from which the presence of binuclear cells can be identified. The intensities of the cytoplasmic versus nuclear component are binary in that the nuclei are gray while the cytoplasm is white. In Figure 1B, it is the opposite: cytoplasm is black while nuclei are white; the different types of stainings used in each Figure represent a different threshold for identifying bi-nuclear cells. Figure 1A represents normal hepatocytes while Figure 1B represents regenerated hepatocytes. The binucleation index for the regenerating liver is less than 4%. The difference between the number of nuclei in each picture is the effect of differences in cytokinesis between each cell type.

Figures 1A and 1B expose a population of cells to a plurality of treatments, capture images of the plurality of cells, obtain a plurality of features from the image, analyze the plurality of cellular features (which include nuclear and cytoplasmic features) to determine the presence of bi-nuclear features. Figures 1A and 1B show determination of bi-nuclear cells from two types of image analyses.

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Table 1 shows the classification of treatments for normal liver versus regenerating liver cells as stated in the title, "Proliferation and binucleation of hepatocytes from regenerating and normal rat liver." Table 1 also applies a statistical test termed a "Binucleation index" indicating abundance of bi-nuclear cells in treated versus a controlled population.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 15, 16, 35, 36, 48-50, and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerlyng et al [Cytometry, volume 13, pages 404-415, 1992] in view of Koss et al. [American Journal of Clinical Pathology, 1998, volume 109, pages 549-557].

15. A computer program product comprising a machine readable medium on which is provided program instructions for identifying bi-nuclear cells from a captured image of a plurality of marked cells, the instructions comprising: code for processing the first image to obtain at least a first feature for each of the plurality of cells; code for analyzing the first features for the plurality of cells to determine whether the first feature is indicative of a bi-nuclear cell; and code for identifying those cells for which the first feature is indicative of bi-nuclear cells as being bi-nuclear cells.

16. A computing device comprising a memory device configured to store at least temporarily program instructions for identifying bi-nuclear cells from a captured image of a plurality of marked cells, the instructions comprising: code for processing the first image to obtain at least a first feature for each of the plurality of cells; code for analyzing the first features for the plurality of cells to determine whether the first feature is

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indicative of a bi-nuclear cell; and code for identifying those cells for which the first feature is indicative of a bi-nuclear cell as being bi-nuclear cells.

35. A computer program product comprising a machine readable medium on which is provided program instructions for characterising cells, the instructions comprising: code for determining, from a captured image of a nuclear component of a plurality of cells, the number of concave portions in the outline of the image of the nuclear component; and code for characterising the cell based on the number of concave portions.

36. A computing device comprising a memory device configured to store at least temporarily program instructions for characterising cells, the instructions comprising: code for determining, from a captured image of a nuclear component of a plurality of cells, the number of concave portions in the outline of the image of the nuclear component; and code for characterising the cell based on the number of concave portions.

48. A computer program product comprising a machine readable medium on which is provided program instructions for identifying bi-nuclear cells, the instructions comprising: code for identifying, from a captured image of a nuclear component of a plurality of cells, at least one pair of nuclear components; code for determining, from a captured image of a cytoplasmic component of the plurality of cells, a measure of the amount of the cytoplasmic component interposed between the pair of nuclear components; and code for characterising the cells based on the measure of the amount of the cytoplasmic component.

49. A computing device comprising a memory device configured to store at least temporarily program instructions for identifying bi-nuclear cells, the instructions comprising: code for identifying, from a captured image of a nuclear component of a plurality of cells, at least one pair of nuclear components; code for determining, from a captured image of a cytoplasmic component of the plurality of cells, a measure of the amount of the cytoplasmic component interposed between the pair of nuclear components; and code for characterising the cells based on the measure of the amount of the cytoplasmic component.

50. A method for identifying biologically relevant pairs of nuclei, comprising: identifying, from a captured image of a nuclear component of a plurality of cells, at least one pair of nuclear components; identifying, from the captured image, a nearest neighbour nuclear component to the pair of nuclear components; and characterising the cells associated with the pair of nuclear components based on the separation of the pair of nuclear components and the separation of the next nearest neighbour nuclear component from the pair of nuclear components.

59. A computer program product comprising a machine readable medium on which is provided program instructions for identifying biologically relevant pairs of nuclei, the

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instructions comprising: (a) code for identifying, from a captured image of a nuclear component of a plurality of cells, at least one pair of nuclear components; (b) code for identifying, from the captured image, a nearest neighbour nuclear component to the pair of nuclear components; and (c) code for characterising the cell associated with the pair of nuclear components based on the separation of the pair of nuclear components and the separation of the next nearest neighbour nuclear component from the pair of nuclear components.

60. A computing device comprising a memory device configured to store at least temporarily program instructions for identifying biologically relevant pairs of nuclei, the instructions comprising: code for identifying, from a captured image of a nuclear component of a plurality of cells, at least one pair of nuclear components; code for identifying, from the captured image, a nearest neighbour nuclear component to the pair of nuclear components; and code for characterising the cell associated with the pair of nuclear components based on the separation of the pair of nuclear components and the separation of the next nearest neighbour nuclear component from the pair of nuclear components.

While Gerlyng et al. teach the limitations of the base claims of processing and analyzing bi-nuclear images, Gerlyng et al. do not teach the method of using a computer program product or device to perform the claims.

Koss et al. teach such a method of computerization, as stated on page 550, column 1, lines 27-29, "The PAPNET system is an interactive, computer-based, semiautomated optical system, previously described in detail,..." The methods section continues to describe such a computerized system of analysis of images.

Thus, it would be obvious to someone of ordinary skill in the art at the time of the instant invention to use manual method of identifying binuclear cells of Gerlyng et al. in view of Koss et al. because Koss et al. have the advantage of application of the manual system in a computerized environment.

Claims 23-25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerlyng et al [Cytometry, volume 13, 1992, pages 404-415] in view of Rumbaugh [USPAT 4,821,210].

Claims 23-25 and 27 state:

23. A method for characterising cells, comprising: determining, from a captured image of a nuclear component of a plurality of cells, the number of concave portions in the outline of the image of the nuclear component; and characterising the cell based on the number of concave portions.

24. The method as claimed in claim 23, further comprising smoothing the outline of the image of the nuclear component.

25. The method as claimed in claim 23, further comprising identifying a concave portion in the outline of the image of the nuclear component by determining the angle subtended by adjacent portions of the outline.

27. The method as claimed in claim 24, wherein smoothing the outline of the image of the nuclear component includes converting the outline into a polygon.

The methods of the base claim of characterizing cells are taught by Gerlyng et al. However, Gerlyng et al. does not teach fitting polygons to cellular structures.

In Rumbaugh, column 7, lines 48-53, it is stated, "generating for each test cell none, one or a set of polygonal representation surfaces which approximate the object corresponding to each cell, which polygons are then sequentially displayed based on a user defined viewplace or angle of viewing to cumulatively form the 3-D object or body."

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice Gerlyng in view of Rumbaugh, for while Gerlyng teaches a method of analysis of bi-nuclear cells, Rumbaugh teaches the advantage of using geometric analysis to simplify line shape around a cell.

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Claims 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerlyng et al [Cytometry, volume 13, 1992, pages 404-415] in view of Miyano et al [USPGPUB 2003/0108230].

Claims 23 and 24 state:

23. A method for characterising cells, comprising: determining, from a captured image of a nuclear component of a plurality of cells, the number of concave portions in the outline of the image of the nuclear component; and characterising the cell based on the number of concave portions.

24. The method as claimed in claim 23, further comprising smoothing the outline of the image of the nuclear component.

The methods of the base claim of characterizing cells are taught by Gerlyng et al. However, Gerlyng et al. does not teach smoothing the structures of the nuclei.

This additional limitation is taught in Miyano et al paragraph [0061] and Figure 11. The process of unifying nucleus area involves drawing an approximate circle around the nucleus as is shown in each picture in Figure 11.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice Gerlyng in view of Miyano, for while Gerlyng teaches a method of analysis of bi-nuclear cells, Miyano teaches the advantage of using geometric analysis to smooth the area around a nucleus.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re*

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Ockert, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-60 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-60 of copending Application No. 10/563,613. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. The claims between the instant and applied application are identical in their entirety.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(f) he did not himself invent the subject matter sought to be patented.

Claims 1-60 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

For the reasons discussed above, it is apparent that copending Application No. 10/563,613 contains claimed subject matter in claims that is not patentably distinct from instant claim 1. Because the inventive entity of copending Application 10/563,613 is different from the instant application, a rejection is appropriate under 35 U.S.C. 102(f). This rejection could be overcome by amendment of the appropriate claims so that the claims are patentably distinct, or by filing a declaration stating the inventive entity for the commonly claimed subject matter is identical.

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Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Ardin Marschel, Ph.D., Supervisory Patent Examiner, can be reached at (571) 272-0718.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

-RSN 3/7/2006

RSN 3/7/06

John S. Brusca 7 March 2006

JOHN S. BRUSCA, PH.D.
PRIMARY EXAMINER